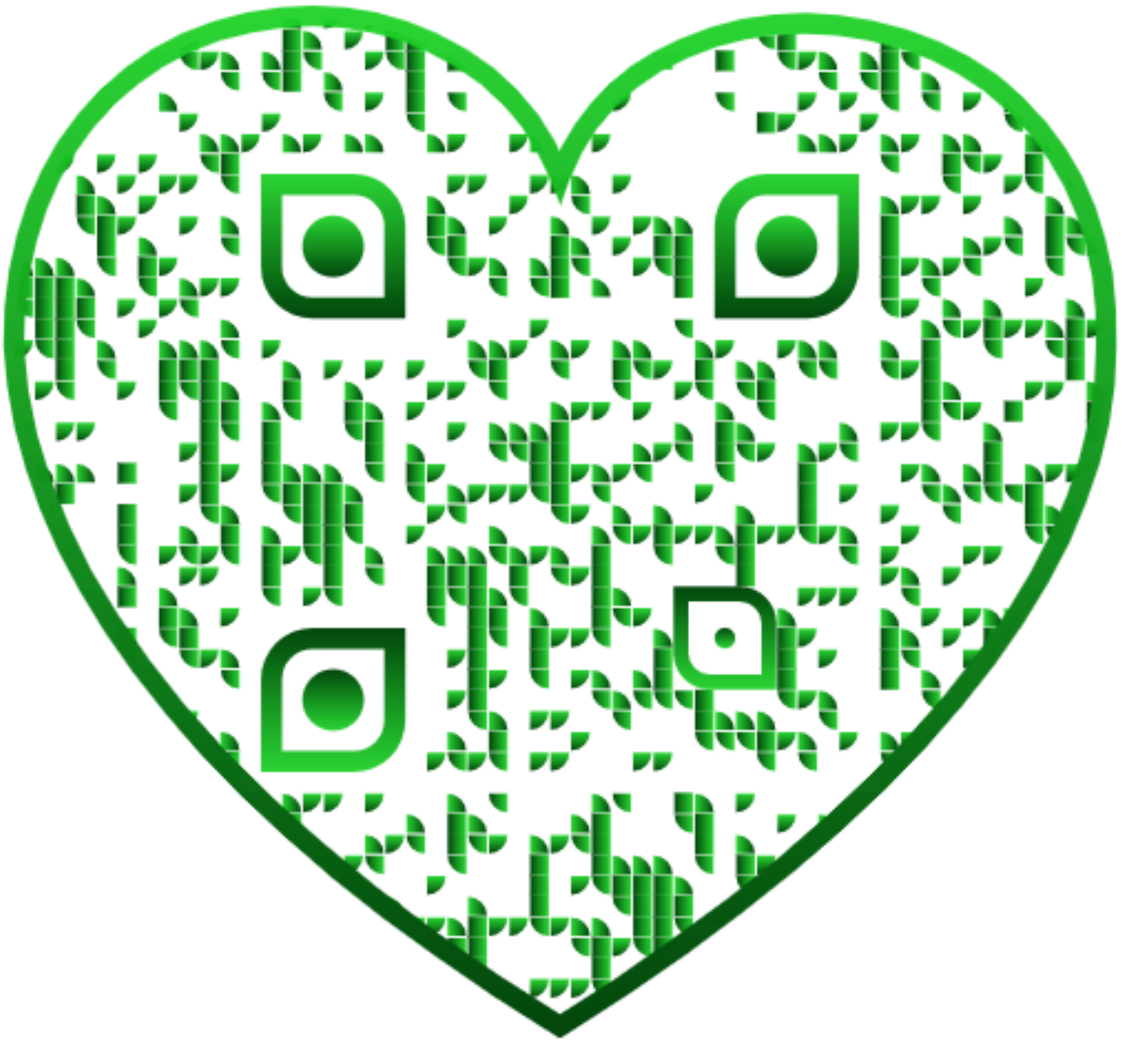
2.5 PK of IV bolus administration



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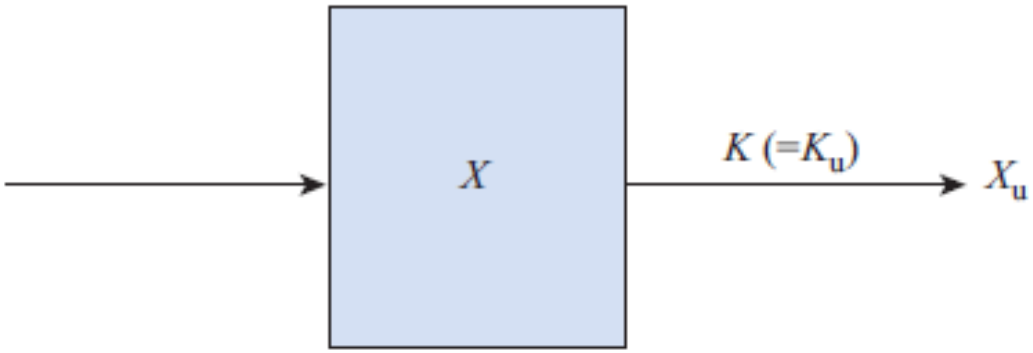
- Assumption
  - One-compartment model, first-order process and passive diffusion are operative,
  - No metabolism takes place (elimination is 100% via renal excretion),
  - The drug is being monitored in blood (plasma/serum) and urine.



- Where,
  - X, mass (amount) of drug in the blood/body at time, t;
  - Xu, mass (amount) of unchanged drug in the urine at time, t;
  - K, first-order elimination rate constant.

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- Useful pharmacokinetic parameters include:
  - Apparent volume of distribution
  - Elimination half life
  - Elimination rate constant
  - Systemic clearance.

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- The above parameters are computed using data either from:
  - Drug concentrations in the plasma, or
  - Urinary excretion data

Drug concentrations in the Plasma

- Following rapid IV injection of a drug that distributes in the body according to a one-compartment model and is eliminated by apparent first-order kinetics,
  - The rate of loss of drug from the body is given by:

$$\frac{dX}{dt} = -KX$$

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- The integration of the above equation gives;

$$X = X_O e^{-Kt}$$

- And dividing both sides by a volume term;

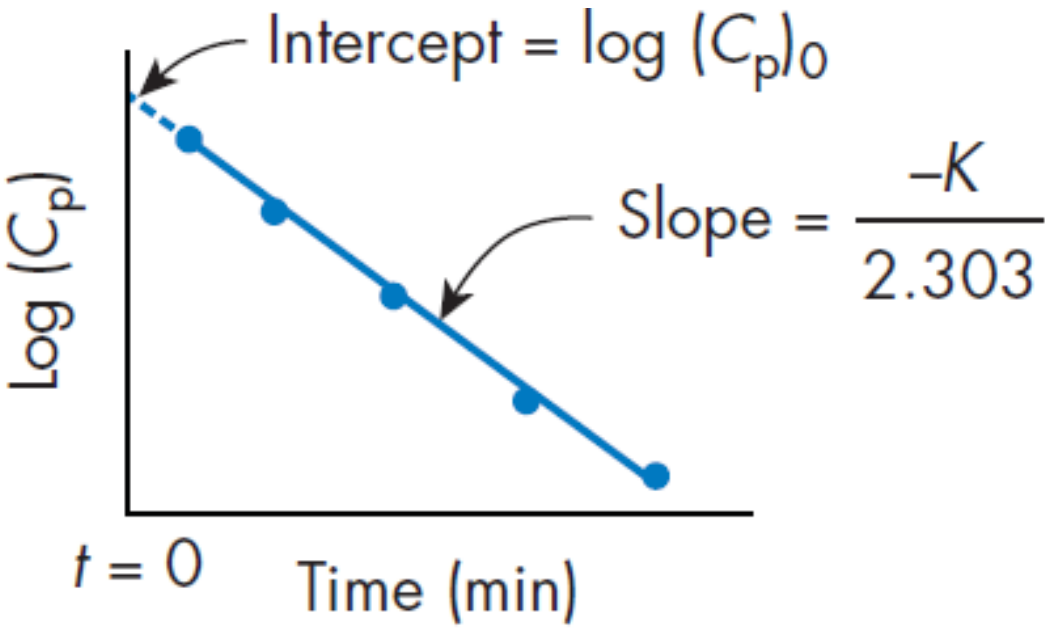
$$\frac{X}{V} = \frac{X_O}{V} e^{-Kt}$$

- Yields;

$$C = C_O e^{-Kt}$$

1. Apparent volume of distribution (V)

- A plot of (logC vs. t) will be linear under the conditions stated.



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- C_O may be obtained by extrapolation of $\log C$ vs. t plot to zero.
- This intercept, C_O, may be used in the calculation of the apparent volume of distribution.
- Since Xo equals the amount of drug injected IV (i.e., IV dose), then:

$$V = \frac{X_O}{C_O} = \frac{IV\ dose}{C_O}$$

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2. Elimination half life ($t_{1/2}$)

- $\boldsymbol{t_{1/2}}$ is readily determined from a semi-logarithmic plot of C_p vs t.

- The Eqn. $\boldsymbol{t_{1/2}}=\frac{0.693}{K}$ is easily derived by setting C = $C_O/2$ and t = $\boldsymbol{t_{1/2}}$ in '$\log C = \log C_O - \frac{Kt}{2.303}$'

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3. Elimination rate constant (K)

- The slope of the line resulting from a plot of log C vs. t is equal to $-\frac{Kt}{2.303}$ and K may be estimated directly from this slope.

- K can also be obtained rearranging the equation:

$$\log C = \log C_O - \frac{Kt}{2.303}$$

- It is easier, however, to estimate K from the relationship:

$$K = \frac{0.693}{t_{1/2}}$$

Drug concentrations in the Urine

- It is sometimes possible to determine the elimination kinetics of a drug from urinary excretion data.
- This requires that at least some of the drug be excreted **unchanged**.

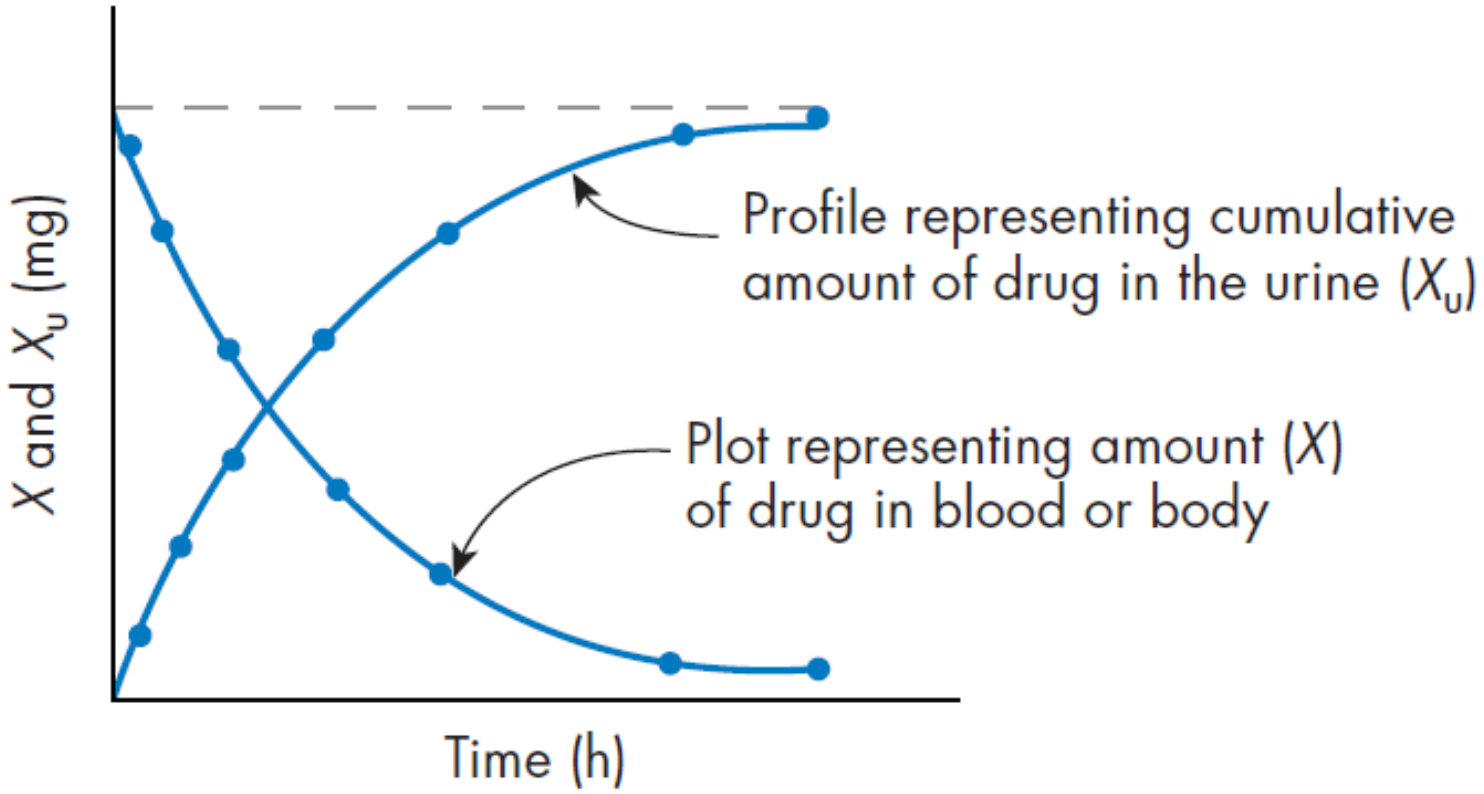
X and X_u (mg)
Time (h)
Profile representing cumulative amount of drug in the urine (X_u)
Plot representing amount (X) of drug in blood or body

Fig. Plot illustrating the amount of drug remaining in the blood and the amount of drug eliminated in the urine with time following the administration of a drug as an intravenous bolus.

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- Advantages
  - Urine collection is a non-invasive technique.
  - A more convenient method of sample collection, and sample size is generally not a problem.
  - Urinary data allows direct measurement of bioavailability.

- Assumptions:
  - One-compartment open model with the entire dose eliminated as unchanged drug
  - First-order process and passive diffusion
  - $(X_u)_\infty = X_O$ (at $t = \infty$)
  - K = K_u (drug is exclusively eliminated by excretion by kidney)

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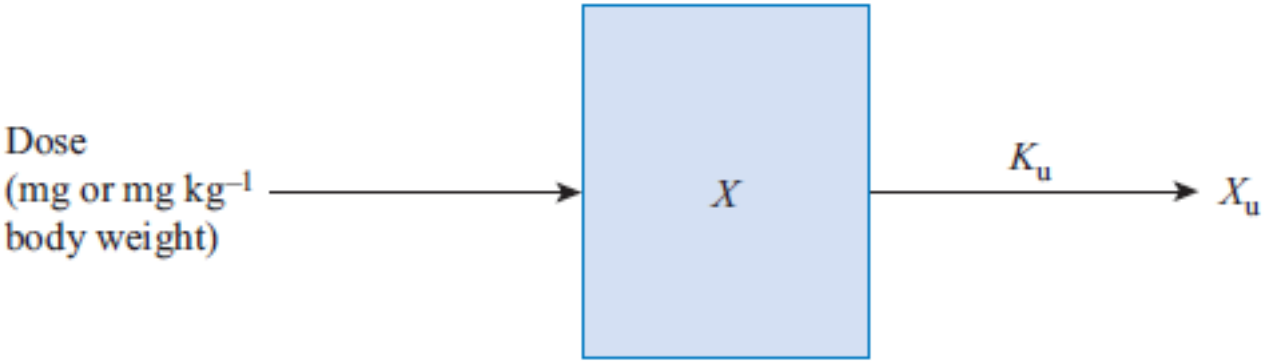
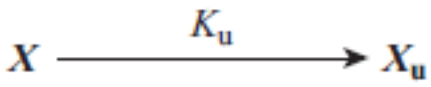


SETUP



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- There are **two methods** that permit us to compute some pharmacokinetic parameters from urinary excretion data.

    1. The rate of excretion method.

    2. The "amount remaining to be excreted" method (ARE); also known as the sigma-minus method

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Rate of excretion method

- The rate of appearance of intact drug in the urine is proportional to the amount of drug in the body,

$$\frac{dX_u}{dt} = K_u X$$

Where, $\frac{dX_u}{dt}$=rate of excretion, X is the amount of drug in the body at time t, X_u is the cumulative amount of drug excreted into urine at time t, and K_u is the excretion/elimination rate constant

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- Substitution for X according to Eqn. $X = X_o e^{-Kt}$ yields

$$\frac{dX_u}{dt} = K_u X_O e^{-Kt}$$

- Therefore, taking the log of the above Eq.,

$$\log \frac{dX_u}{dt} = \log K_u X_O - \frac{Kt}{2.303}$$

- Note, $K=K_u$

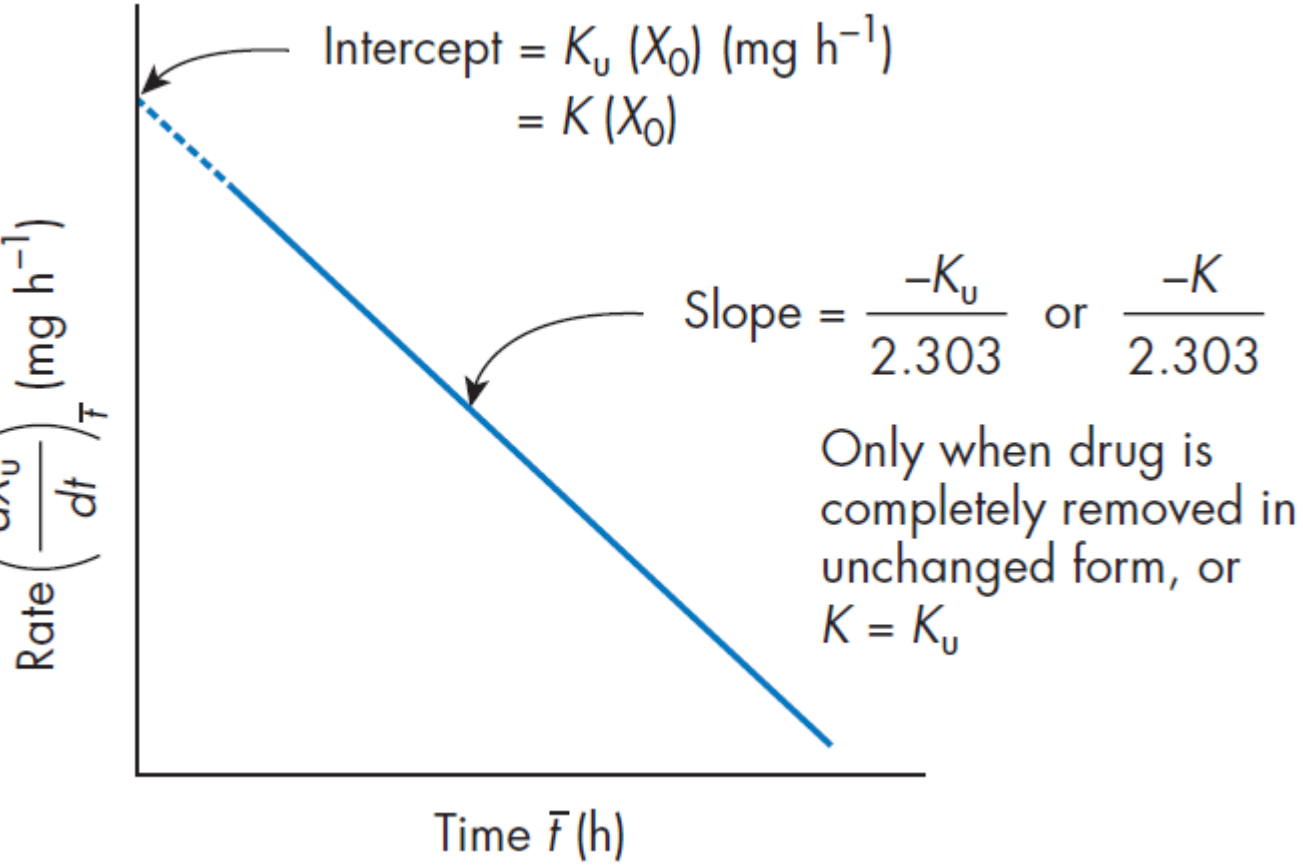
Intercept = K_u (X_0) (mg h^{-1})
= K (X_0)
Slope = $\frac{-K_u}{2.303}$ or $\frac{-K}{2.303}$
Only when drug is completely removed in unchanged form, or $K = K_u$
Rate $\left(\frac{dX_u}{dt}\right)_{\bar{t}}$ (mg h^{-1})
Time $\bar{t}$ (h)

Fig. Semi log plot of excretion rate vs. t after IV administration of a drug.

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- Eqn. states that a semi log plot of excretion rate of un-metabolized drug versus time is linear, with a slope of $-\frac{K}{2.303}$.

- This slope is the same as that obtained from a semi log plot of C_p vs. t.

- Thus, the elimination rate constant of a drug can be obtained from either plasma concentration or urinary excretion data.

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- Urinary excretion rates are estimated by:
  - Collecting all urine for a fixed period of time,
  - Determining the concentration of drug in the urine,
  - Multiplying the concentration by the volume of urine collected to determine the amount excreted, and
  - Dividing the amount excreted by the collection time.

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- Table: Calculation of excretion rate vs. time data for estimating half-life.

t (h)	X_u (mg)	Δt	ΔX_u	$\Delta X_u/\Delta t$ (mg/h)	t_m
0	0.0				
		1	4.0	4.0	0.5
1	4.0				
		1	3.8	3.8	1.5
2	7.8				
		1	3.5	3.5	2.5
3	11.3				
		3	9.1	3.0	4.5
6	20.4				
		6	13.5	2.2	9.0
12	33.9				
		12	14.7	1.2	18.0
24	48.6				
		12	6.4	0.53	30.0
36	55.0				
		12	2.8	0.23	42.0
48	57.8				

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- These experimentally determined excretion rates are obviously not instantaneous rates (i.e., $\frac{dX_u}{dt}$), but are average rates over a finite time period (i.e., $\frac{\Delta X_u}{\Delta t}$).

- However, we often find that $\frac{\Delta X_u}{\Delta t}$ closely approximates $\frac{dX_u}{dt}$ at the midpoint of the urine collection period.

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- Limitation of the rate of excretion method
  - Fluctuations in the rate of drug elimination are reflected to a high degree in excretion rate plots.
  - At times, the data are so scattered that an estimate of the half-life is difficult.
- To overcome this problem, an alternative approach, termed the **sigma-minus method**, is available.

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The amount remaining to be excreted (sigma minus) method

$$\frac{dX_u}{dt} = K_u X$$

Where, X is the amount of drug in the body at time t, X_u is the cumulative amount of drug excreted into urine at time t, and K_u is the excretion/elimination rate constant

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- Integrating the above equation ($\frac{dX_u}{dt} = K_u X$)

$$X_O - (X_u)_t = X_O e^{-K_u t}$$

- When $t = \infty$, $(X_u)_\infty = X_O$ (dose)

$$(X_u)_\infty - (X_u)_t = X_O e^{-K_u t}$$

- $(X_u)_\infty - (X_u)$ is the amount of drug remaining to be excreted (ARE)

- A plot of ARE vs. t is a straight line

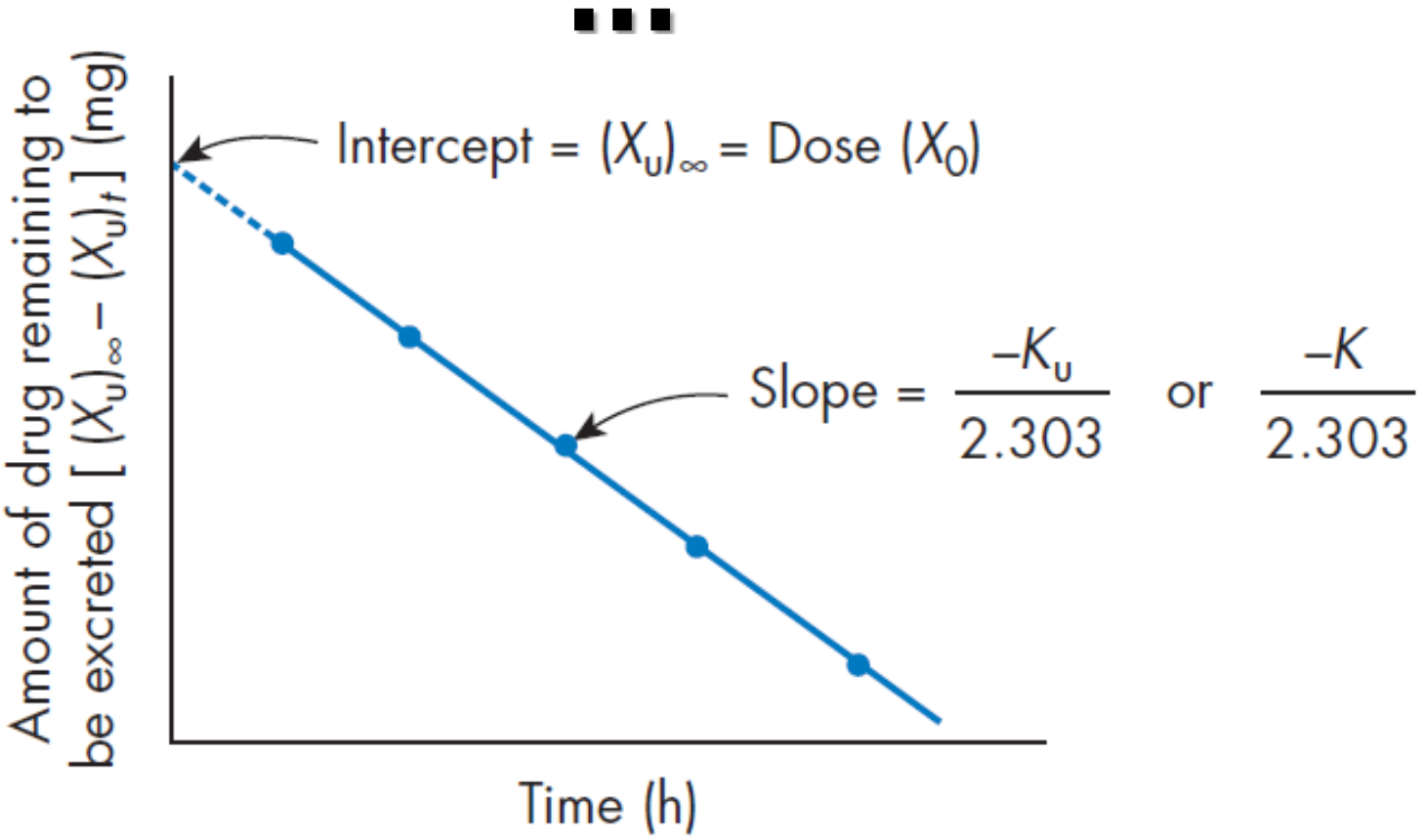

Fig. Semi log plot of ARE vs. t after IV administration of a drug (On a semilog paper).

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- The slope of the graph permits the determination of the excretion rate constant which is equal to the elimination rate constant.
  - We can also obtain the elimination half life
  - The intercept is $(X_u)_\infty \; or \; X_O$ (dose).
    - This is true only when there is an absence of metabolite(s)

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- Limitations of the ARE method:
  - Urine samples must be collected until such time that, practically, no additional drug appears in the urine (i.e. t = 7 $t_{1/2}$)
  - No urine samples can be lost (the exact volume of urine at each time interval must be known)
  - This is a time-consuming (especially for a drug with a long $t_{1/2}$)
  - There is a cumulative build up of error.

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- In general, elimination rate constant may be estimated from plots of
  - log drug concentration in plasma versus time,
  - log excretion rate versus time (the rate method), and
  - log A.R.E. versus time (the sigma-minus method).

Estimating Renal Clearance

- The kinetics of renal excretion of a drug may be characterized not only by a renal excretion rate constant K_u, but also by a renal clearance CL_R.

- By definition, CL_R is simply the ratio of urinary excretion rate to drug concentration in the blood or plasma:

$$CL_R = \frac{dX_u/dt}{C} = \frac{K_u X}{C}$$

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- Recognizing that $\frac{X}{C}$ is simply the apparent volume of distribution we can write:

$$CL_R = K_u \times V$$

- An estimation of CL_R by means of '$\frac{dX_u/dt}{C}$' may be misleading because like all rate processes in the body, renal excretion is subject to biologic variability.

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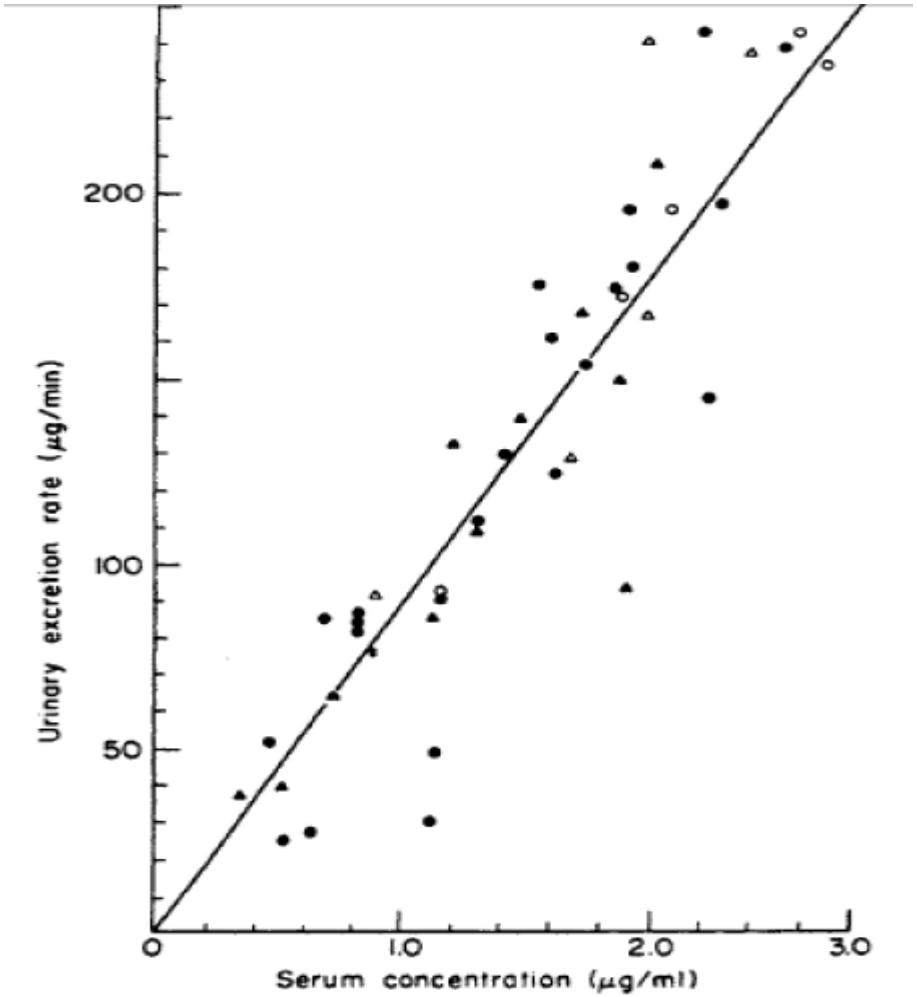
- A more satisfactory approach is to plot ${}^{dX_u}/_{dt}$ vs. C at the midpoints of the urine collection periods.

- Since,

$$\frac{dX_u}{dt} = CL_R \times C$$

- The slope of an excretion rate-plasma concentration plot is equal to renal clearance.


Urinary excretion rate (μg/min)
200
100
50
0
1.0
2.0
3.0
Serum concentration (μg/ml)

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Systemic Clearance

- It has been shown that the product of the urinary excretion rate constant K_u and V is equal to renal clearance.
- The product of the elimination rate constant K and V also yields a clearance term, **systemic clearance** (CL_S).
- It can be shown that the systemic clearance is given by the ratio of the IV dose to the AUC.

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- Since,

$$CL_R = K_u.V = \frac{X_u^\infty}{AUC}$$

- Then,

$$V = \frac{X_u^\infty}{K_u \times AUC}$$

- And, at $t = \infty$, $X_u^\infty = X_O$, and for a drug excreted only renaly, $K_u = K$

...

- Therefore,

$$V = \frac{X_O}{K \times AUC} = \frac{CL_s}{K}$$

- And,

$$CL_s = V.K$$